Studies on the network biology impact in pharmacology and toxicology

Jian Tao[1*]

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[1]School of Computer Science and Engineering, Qujing Normal University, Qujing 655011, China

*Corresponding author: jian087@gmail.com.

Network biology is a concept to deals with the biological process on a broader level. The molecular interactions at the cellular level are considered as a network. The aims of network biology are to investigate the components of cellular networks and their interactions. These approaches are widely used in pharmacology and toxicology. The current reports explore the area of application of network biology to understand drug action and drug development studies. Quantitative systems pharmacology (QSP) is a very useful approach to understanding the drug action at the individual level. Systems Recent advances of technology enable toxicology for the understanding toxin effect in the molecular network. Several genetics and epigenetic approaches are used to understand the biological network. Systems pharmacology or system toxicology approaches have enormous prospects for target-based drug design and understanding the adverse side effect or drug resistance in different pathological conditions.

Keywords: *Network, System biology, Database, Pharmacology, Toxicology*

1. Introduction

Biological systems are heterogeneous in nature and are defined as networks of complex molecular interaction among molecules. The main purpose of network biology is to explore biological pathways at the systemic level and analysis of data to develop a model [1]. Recent advances in genomics and proteomics technologies and the availability of large sets of biological data help to understand the biological process like metabolomics, transcriptomics, and other interatomic (protein-protein interaction, protein-DNA interaction, protein-drug, etc) at the systemic level. In general, toxicology or pharmacology deals with the interaction of small molecules inhibitors (drugs/inhibitors) on biological pathways. A “one disease-one target-one drug” approach was the common practice in drug discovery but this created problems at the systemic level and caused off-targeting [2]. Network biology approaches utilize a large amount of available biological and chemical data along with bioinformatics to understand the mechanism of drugs and their effect on the system. Moreover, mathematical modeling based on biological experimental data in network biology provides new

hypotheses as well predictions of new mechanistic pathways for the intervention of pharmacology and toxicology studies [3].

2. Review of Literature

2.1. Networks

The network is an important concept to understand systems biology. Networks are best represented by graph theory that consists of nodes and edges. Biological networks are defined as binary interactions or relations between different biomolecules. Network biology deals with the structure, function, regulation of various biological networks. It is an interdisciplinary science based on life sciences, mathematics, computational and statistics [4]. Aims of network biology is to investigate the components of cellular networks and their interactions. These approaches are widely used in various disciplines of biomedical research including pharmacological and toxicological studies for various diseases. Network biology aims to understand biological entities not only as individual components but also at a systemic level. In biomedical studies, experimental high-throughput data were processed by computational and theoretical methods to establish a model [5]. Several networks in biological systems are the target for drug discovery and vaccine development. Pharmacology and toxicology research mainly focused on the biological networks discussed below.

2.2. Network in proteomes

Protein-protein interaction networks (PPI) define the physical interaction among proteins present inside the cell. These interactions are essential for cellular processes and regulate several cellular metabolic pathways [6]. Regulation of enzymes is also modulated by protein-protein interaction which leads to altering the function of the biological network. Yeast two-hybrid system is the traditional method for studying binary interactions. High throughput mass spectrometry studies are used for protein-protein interaction in the characterization of the networks in biological systems.

2.3. Network in transcriptomes

Gene encodes transcripts (RNA) which are crucial factors for the regulation of various networks. Messenger RNA (mRNA) encodes proteins the key player for the metabolic network. Besides these, other RNA like tRNA, rRNA and various small RNA playsa major role in the regulation of biological networks. RT-PCR is the main technique for the identification of genes. Next Generation DNA sequencing (NGS) provides enormous information for the genetic data [7]. The effect of proteins in the regulation of transcriptomes can be evaluated by several high throughput techniques like CHIP-seq, CLIP etc.

2.4. Networks in Pharmacology

The action of drugs acting on biological systems and its response in the body is the major aspect of pharmacology. Drugs may be defined as molecules (natural products, synthetic origin) that exert a physiological effect on organisms at the cellular level. Pharmacology integrates the knowledge of many disciplines for the betterment of human health. Systems pharmacology is the applied version of pharmacology that deals with drugs acting on the human body at a systemic level [8]. Systems pharmacology encounters the

effect of a drug in the form network of interactions. These approaches allow the understanding of the adverse pathological effect to the individual patient and also for new targets [9]. Identification of additional targets (off-targets) for drugs can subsequently lead to improved drug development to decrease off-target effects and potential repurposing of existing drugs for different diseases. Quantitative systems pharmacology (QSP) is introduced as a discipline for the characterization of disease processes and drug action. QSP is used for

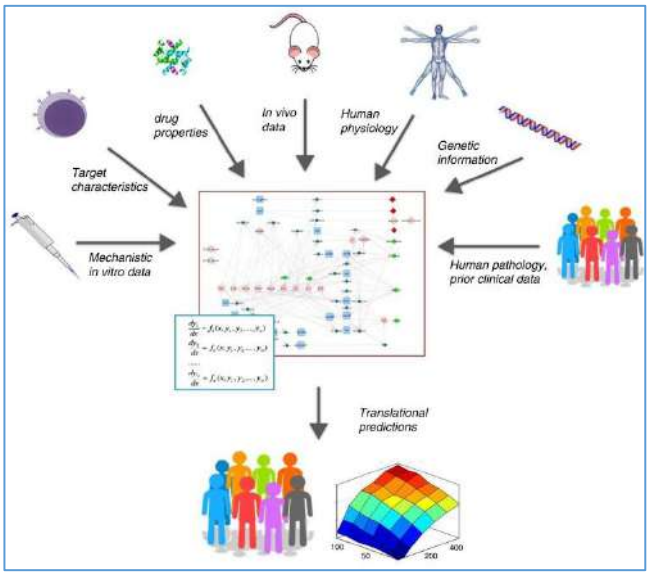

Figure 1: Figure 1: Schematic diagram for systems pharmacological analyses. Several systems are considered for the global analysis. Data were processed and fitted to the appropriate mathematical model for translational predictions.

therapeutic intervention assessment of disease considering the system-wide dynamics of molecular mechanisms of pathogenesis ad therapeutics. QSP is increasingly being used for this purpose in pharmaceutical research & development to help guide the discovery and development of new therapeutics. QSP models are very useful approaches to understand the response of drugs on the level of multiple pharmacodynamics (PD) markers [10].

2.5. Networks in Toxicology

Toxicology is the field of science that deals with the harmful effects of chemicals in our body. It is a multidisciplinary subject that cover several subjects including chemistry, physiology, pharmacology etc. Dosage and Duration are the two important parameters for toxicology. Besides this other parameters include route of exposure, species, age, sex, and environmental conditions [11]. Toxicology is currently used in cancer chemotherapy since some toxins can be used as anti-cancer chemotherapy. Toxicological studies predict the adverse effects of drugs and other xenobiotics.

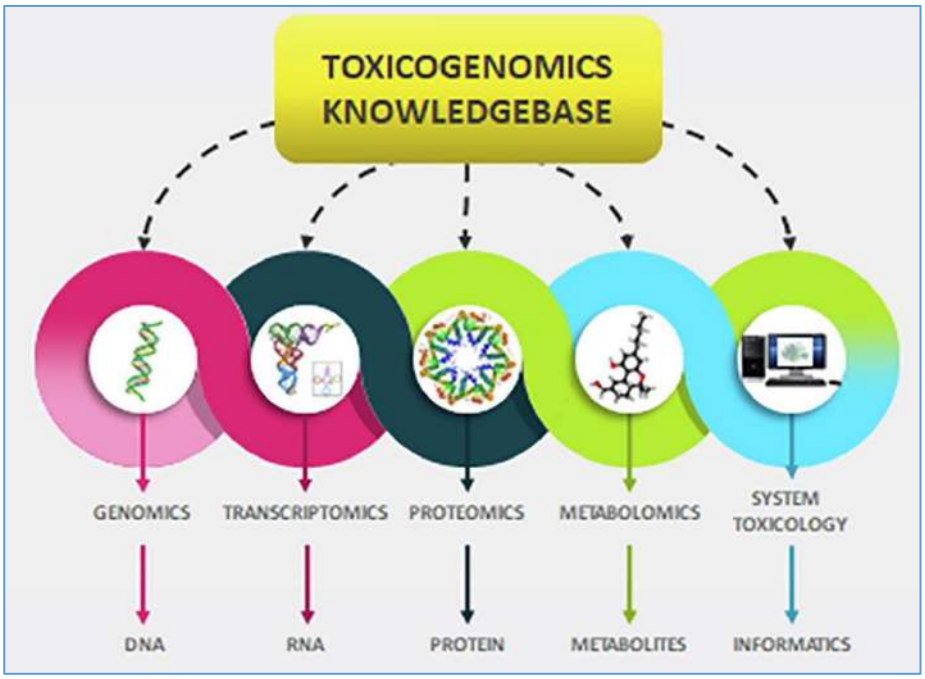

Figure 2: Schematic diagram of toxicogenomics. Toxicogenomics deals with the effect of chemicals (drugs, toxin, small molecule inhibitors etc) on multiple aspects cellular process at the systemic level. Genomicsdeals with DNA, Transcriptomics deals with RNA, Proteomics deals with proteins and Metabolomics deals with changes in metabolic pathways [12].

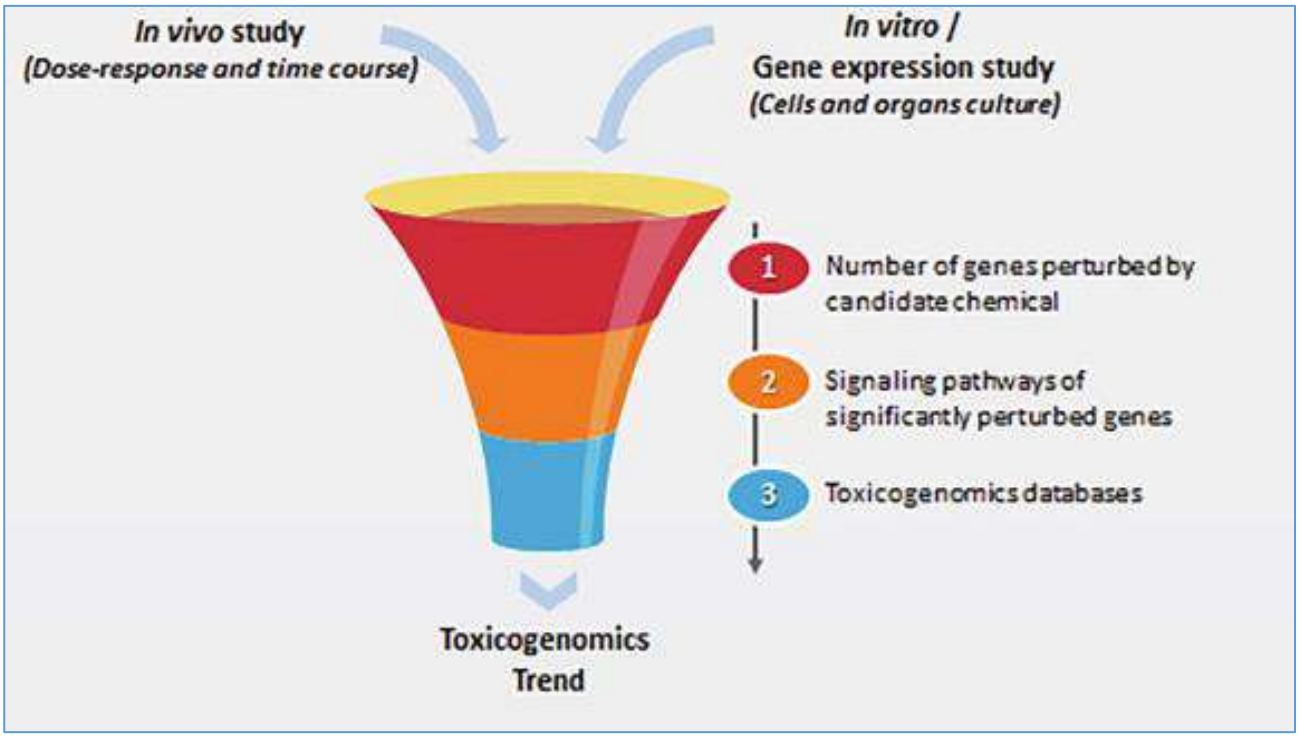

Figure 3:Flow diagram of toxicogenomics. Data collected from different experimental methods from in vivo and invitro studies. The number of gene expression are checked by the treatment chemicals/xenobitics. Alteration of signaling pathways are also monitored [12]. Data are analyzed to make model for the perdition of mechanism of drug action

The tremendous complexity of these networks makes it difficult to understand the effects of xenobiotics on their ability to function. Systems Toxicology is the combination of conventional toxicology with system biology of molecular pathways. Systems toxicology defines the -omics in a biological system by several ways e.g. alteration of toxicants and stressors, analyzing the toxicological parameters expression. The data obtained from several in vitro, in vivo as well as omics in toxicological studies are not fully utilized because of the lack of a proper predictive model. The understanding of the effects of treatments is generally evaluated in a single system rather than considering the total system network. For accurate prediction and comprehensive integration of large sets of data, a mathematical robust model is required.

Systems toxicology defines the overall system network in computational approaches to address the effect of toxins on the system.

2.6. Proteomics and genomics in network biology

The systematic and quantitative molecular analysis of drug action on the molecular pathways are achieved by proteomic analysis at the systemic level. Mass spectrometry (MS)–based proteomics is a powerful technique to get a wide range of data to interpret the drug action in molecular level. MS-based proteomics has been applied to network biology to identify the nodes and edges of biological networks. Drug actions are characterized in stable isotope labeling of cell line followed by MS analysis [13]. The data obtained from these data were analyzed by gene ontology (GO term) analysis. The go-term analysis is a bioinformatics tool that predicts the enrichment of target proteins on particular drug treatments [14]. This analysis also generate a complex network with the possible metabolic pathways. Next-generation sequencing (NGS) is a robust genetic technique used for system biology. It has potential relevance as a comprehensive pharmacogenetic genotyping platform to identify genetic variation related to drug therapy. NGS approaches can be utilized in pharmacology and toxicology research. These approaches enable to understand the effect of drugs or toxins on the system in the transcriptomics level. Global transcriptomics data provide enormous information for its intermoics studies. Moreover, NGS will also explore the mechanism of drug resistance by mutational analysis of the transcripts.

3. Conclusions

Network biology is the growing discipline for modern biomedical research and it has immense translational application in pharmacology and toxicology. The data obtained from both actual experimental and computational *in silico* studies are analyzed by this platform to provide a model for further prediction of the mechanism of drug actions. Recent advent of molecular genetics approaches like gene knock out, knockdown etc make the system more convincing to further study of drug action in the cellular level. Moreover knock-out animal model is helpful to understand the molecular pathway in total systemic level for pharmacology and toxicology. The complicacy of the onset of diseases like cancer, neurodegenerative diseases, metabolic disorder (diabetes) are needed to be considered at individual patient level. In this perspective the overall biochemical network need to be characterized. Drug action should also be considered in the network not in the

speculated targets. Ultimately, with the adoption of such novel research perspectives, systems pharmacology will prove to become one of the future research platforms for more effective drug development pipeline with the integration of systems-based analysis [15].

References

[1] Redhu, N., & Thakur, Z. (2022). Network biology and applications. In Bioinformatics (pp. 381-407). Academic Press.

[2] Nogales, C., Mamdouh, Z. M., List, M., Kiel, C., Casas, A. I., & Schmidt, H. H. (2021). Network pharmacology: curing causal mechanisms instead of treating symptoms. Trends in pharmacological sciences.

[3] Yadav, B. S., &Tripathi, V. (2018). Recent advances in the system biology-based target identification and drug discovery. Current Topics in Medicinal Chemistry, 18(20), 1737-1744.

[4] Santolini, M., &Barabási, A. L. (2018). Predicting perturbation patterns from the topology of biological networks. Proceedings of the National Academy of Sciences, 115(27), E6375-E6383.

[5] Liu, C., Ma, Y., Zhao, J., Nussinov, R., Zhang, Y. C., Cheng, F., & Zhang, Z. K. (2020). Computational network biology: data, models, and applications. Physics Reports, 846, 1-66.

[6] Braberg, H., Echeverria, I., Kaake, R. M., Sali, A., &Krogan, N. J. (2022). From systems to structure—using genetic data to model protein structures. Nature Reviews Genetics, 1-13.

[7] Camacho, D. M., Collins, K. M., Powers, R. K., Costello, J. C., & Collins, J. J. (2018). Next-generation machine learning for biological networks. Cell, 173(7), 1581-1592.

[8] Azer, K., Kaddi, C. D., Barrett, J. S., Bai, J. P., McQuade, S. T., Merrill, N. J., ... &Baliga, N. S. (2021). History and future perspectives on the discipline of quantitative systems pharmacology modeling and its applications. Frontiers in physiology, 12.

[9] Sher, A., Niederer, S. A., Mirams, G. R., Kirpichnikova, A., Allen, R., Pathmanathan, P., ...& Noble, D. (2022). A Quantitative Systems Pharmacology perspective on the importance of parameter identifiability. Bulletin of Mathematical Biology, 84(3), 1-15.

[10] Aghamiri, S. S., Amin, R., &Helikar, T. (2021). Recent applications of quantitative systems pharmacology and machine learning models across diseases. Journal of Pharmacokinetics and Pharmacodynamics, 1-19.

[11] Barouki, R., Audouze, K., Becker, C., Blaha, L., Coumoul, X., Karakitsios, S., ...&Sarigiannis, D. (2022). The Exposome and Toxicology: A Win–Win Collaboration. Toxicological Sciences, 186(1), 1-11.

[12] Yahya, F. A., Hashim, N. F. M., Ali, D. A. I., Ling, T. C., & Cheema, M. S. (2021). A brief overview to systems biology in toxicology: The journey from in to vivo, in-vitro and–omics. Journal of King Saud University-Science, 33(1), 101254.

[13] Veenstra, T. D. (2021). Omics in systems biology: Current progress and future outlook. Proteomics, 21(3-4), 2000235.

[14] Good, B. M., Van Auken, K., Hill, D. P., Mi, H., Carbon, S., Balhoff, J. P., ...&D'Eustachio, P. (2021). Reactome and the Gene Ontology: Digital convergence of data resources. Bioinformatics, 37(19), 3343-3348.

[15] Kaddurah-Daouk, R., Weinshilboum, R. M., &Pharmacometabolomics Research Network. (2014). Pharmacometabolomics: implications for clinical pharmacology and systems pharmacology. Clinical Pharmacology & Therapeutics, 95(2), 154-167.